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Synthesis of a biphenyl library for studies of hydrogen bonding in the solid state

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ABSTRACT

A biphenyl library incorporating amide and sulfonamide groups has been synthesised via microwave-mediated Suzuki–Miyaura couplings. Many derivatives were crystallised from dichloromethane/methanol and analysed by single crystal X-ray diffraction. An interesting structure was obtained for *N*-(4′-methylbiphenyl-4-yl)acetamide with Z′=6 and hydrogen-bonding networks of the type N–H···O in the unit cell.

1. Introduction

Recent studies from our group have focussed on microwave-mediated cross coupling reactions of arylboronic acids **1** with bromonitroarenes **2** in the synthesis of biaryl libraries with potential applications in medicinal chemistry.[1] Reduction of the nitro compounds **3** affords biphenylamines **4** and, following reaction with acid chlorides **5**, amides **6** can be formed. Of notable interest was *N*-(4′-methylbiphenyl-4-yl)cyclopropanecarboxamide **6a**, which was (i) formed unexpectedly by Pd-catalysed hydrogenolysis of a piperazinyl–methylbiphenyl precursor and (ii) found to be very interesting in the solid state with three molecules in the asymmetric unit (Z′=3), since it contains chains formed by intermolecular N–H···O hydrogen bonds.[2] We now report an unambiguous synthesis of **6a**. Moreover, a related biphenyl library has been synthesised in order to expand the synthetic scope of this reaction as well as to study, in the solid state, analogues of **6a** where a number of parameters have been varied, including the regiochemistry and type of substituents on the biaryl unit (Scheme 1).

The aminobiaryl derivatives **4c**–**f** were purchased as free amines or as the corresponding HCl salts. The biarylamines **4a** and **4b** were synthesised as outlined (Scheme 1) involving a facile microwave-mediated Suzuki Miyaura coupling,[3] to afford **3**, followed by a reduction in the presence of Raney Nickel using a flow reactor[4] with both steps giving excellent yields. Several derivatives **4** were reacted with a range of acid or sulfonyl chlorides **5**, in the presence of solid-supported base (PS-NMM, polystyrene supported morpholine)[5] in order to obtain the corresponding amides or sulfonamide derivatives **6** (Table 1).

The variation of the amide substituents (e.g., *c*-prop vs Ac; **6a** vs **6b**), the regiochemistry on the biphenyl unit (4, 4′ vs 4, 3′; e.g., **6b** vs **6i**) and the replacement of the biphenyl unit by an aryl pyridinyl unit (e.g., **6a** vs **6g**) were investigated. Not only were the amides or related substituents varied around the biphenyl unit but also the methyl group in the 2′ and 3′ position of the biphenyl (e.g., **6k** vs **6l**). A series of amides and sulfonamides **6b**–**n** were synthesised in order to study the resulting compounds in the solid state. A number of positional isomers were synthesised e.g., **6h**–**m**. The benzamide, **6n**, was synthesised to see if a high Z′ value would still be observed in the absence of a second aryl unit in the solid state.

2. Solid state study

The biphenylamides and sulfonamides **6** were obtained in good yields and crystals were grown in order to undertake a solid state study by single crystal X-ray crystallography. Not all of the

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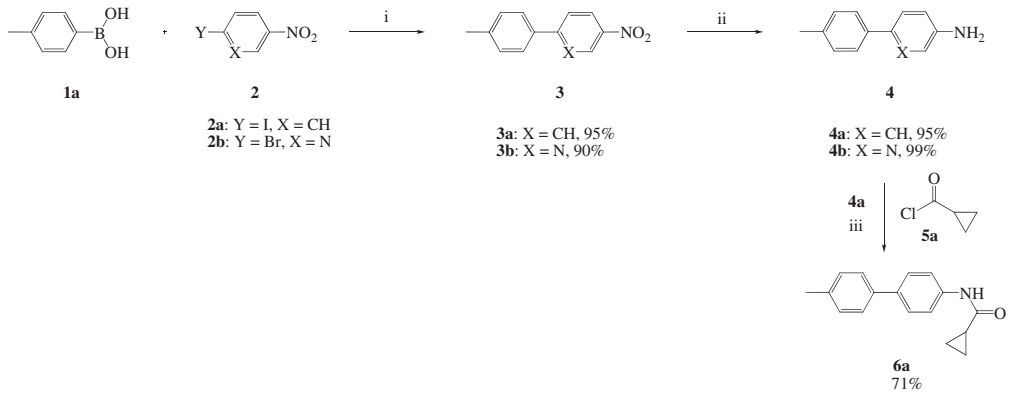
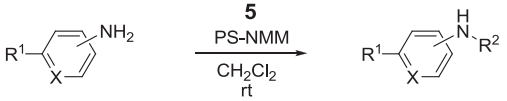
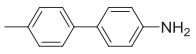
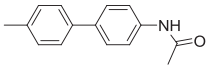
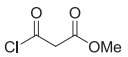
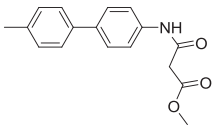
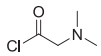
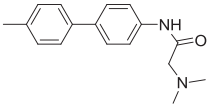
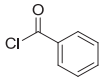
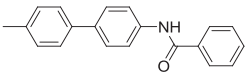
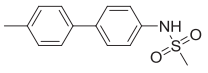
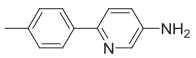
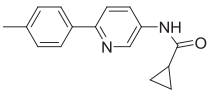
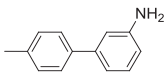
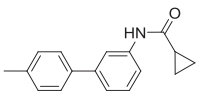


Scheme 1. Synthesis of biarylamines **4** and **6a**. Reagents and conditions: (i) **2** (1.1 equiv), $Pd(PPh_3)_4$ (3 mol %), Na_2CO_3 (3 equiv), toluene/ethanol/water 1:1:1, 150 °C, 10 min, microwave irradiation (power max. 300 W). (ii) H_2, Raney Nickel, H-Cube, EtOH/EtOAc, 65 °C, 0.8 mL/min (iii) PS-NMM (2 equiv) CH_2Cl_2, rt, 16 h.

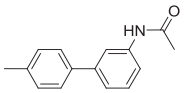
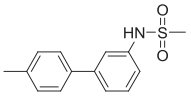
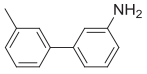
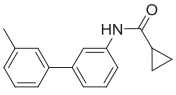
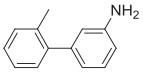
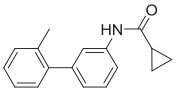
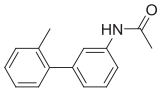
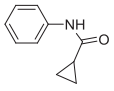
Table 1
NH_2 functionalisation of **4**



Entry	**4**	**5**	Time (h)	Product (**6**)		Yield (%)[a]
1	 **4a**	 **5b**	48		**6b**	99
2	**4a**	 **5c**	16		**6c**	97
3	**4a**	 **5d**	16		**6d**	81
4	**4a**	 **5e**	24		**6e**	91
5	**4a**	 **5f**	24		**6f**	82
6	 **4b**	 **5a**	16		**6g**	34
7	 **4c**	**5a**	16		**6h**	74

(*continued on next page*)

Table 1 (*continued*)

Entry	4	5	Time (h)	Product (**6**)		Yield (%)[a]
8	**4c**	**5b**	16		**6i**	89
9	**4c**	**5f**	16		**6j**	40
10	 **4d**	**5a**	16		**6k**	26
11	 **4e**	**5a**	16		**6l**	52
12	**4e**	**5b**	16		**6m**	46
13	 **4f**	**5a**	16		**6n**	90

[a] Isolated yields after purification by chromatography.

compounds **6** were able to crystallise (e.g., in CH_2Cl_2 or CH_2Cl_2/MeOH 1:1 mixture) in order to yield crystallographic quality samples e.g., the benzamide **6e** was rather insoluble and crystals were unobtainable.

3a is a simple nitrobiphenyl and was studied by X-ray crystallography as a comparator. In its crystal structure, the molecule lies on a twofold axis in the crystal, thus two asymmetric units of atoms are shown, hence the repeat of atom label numbers (Fig. 1).

Most of the compounds in this study gave $Z'=1$ structures. The replacement of a phenyl by a pyridine unit did not lead to higher Z' values. The position of the methyl and the amide groups appears to influence the solid state structure of the biphenylamides, with high Z' values being obtained exclusively for the 4′,4-isomers **6a** and **6b** yet not for the isomeric **6i**, **6k** or **6l**, under the selected crystallisation conditions.

The crystal structure of **6b** was found to be very interesting. The molecules are linked via N–H···O hydrogen bonds and the asymmetric unit consists of six independent molecules ($Z'=6$). This is crystallographically unusual and is likely a metastable 'kinetic' form rather than the most stable thermodynamic structure.[6]

The solid state study of the influence of the regiochemistry and type of functional group in such biphenyls is not a simple exercise; a caveat in our current approach is that the crystal structures obtained are not necessarily influenced solely by the single parameter changes undertaken (regiochemistry, substituents etc.). The crystallisation process has a large influence on crystal formation, including temperature, type of solvent(s) and concentration. Further investigations are currently underway in order to interpret these processes and to complement the current study by the use of a number of physiochemical techniques including thermogravimetric and calorimetric studies and will be reported in due course.[7] Furthermore, many of the compounds described can be considered as 'rule of three' fragments, containing a biphenyl privileged structure, and may have applications in fragment-based drug discovery.[8]

3. Conclusion

We have described the synthesis of a small biaryl library and carried out the determination of eight crystal structures, one of which was noteworthy from a crystallographic point of view in terms of its high Z' value and hydrogen-bonding network.

4. Experimental section

4.1. General information

All reactions were carried out in air, except where specified, and commercial grade solvents and materials were used. NMR spectra were measured on a Jeol ECP400 spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C) in $CDCl_3$ or DMSO-d_6. Microwave reactions were performed in a CEM Discover unit. Chromatographic purifications were carried out on an ISCO purification unit, Combi Flash RF 75 PSI, using Redisep silica gel columns. Purities of compounds were assessed by inspection of their ^{1}H and ^{13}C NMR spectra, TLC on aluminium sheets silica gel 60 F_{254} pre-coated and a large number of solid compounds were analysed by combustion analysis performed on a CE Instruments apparatus Flash EA 1112 Series.

4.2. General procedure for the Suzuki–Miyaura coupling reaction

4.2.1. 4′-Methyl-4-nitrobiphenyl ***3a***.[9] 4-Tolylboronic acid **1** (136 mg, 1.00 mmol), 4-bromo-1-nitrobenzene **2a** (274 mg, 1.10 mmol), *tetrakis*(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol), sodium carbonate (318 mg, 3.00 mmol), toluene (1 mL), ethanol (1 mL) and water (1 mL) were mixed in a microwave vial. The mixture was stirred under microwave irradiation at 150 °C for 10 min (initial power 300 W) then cooled to room temperature, diluted with EtOAc and water and extracted with EtOAc. The separated organic layer was washed with a saturated

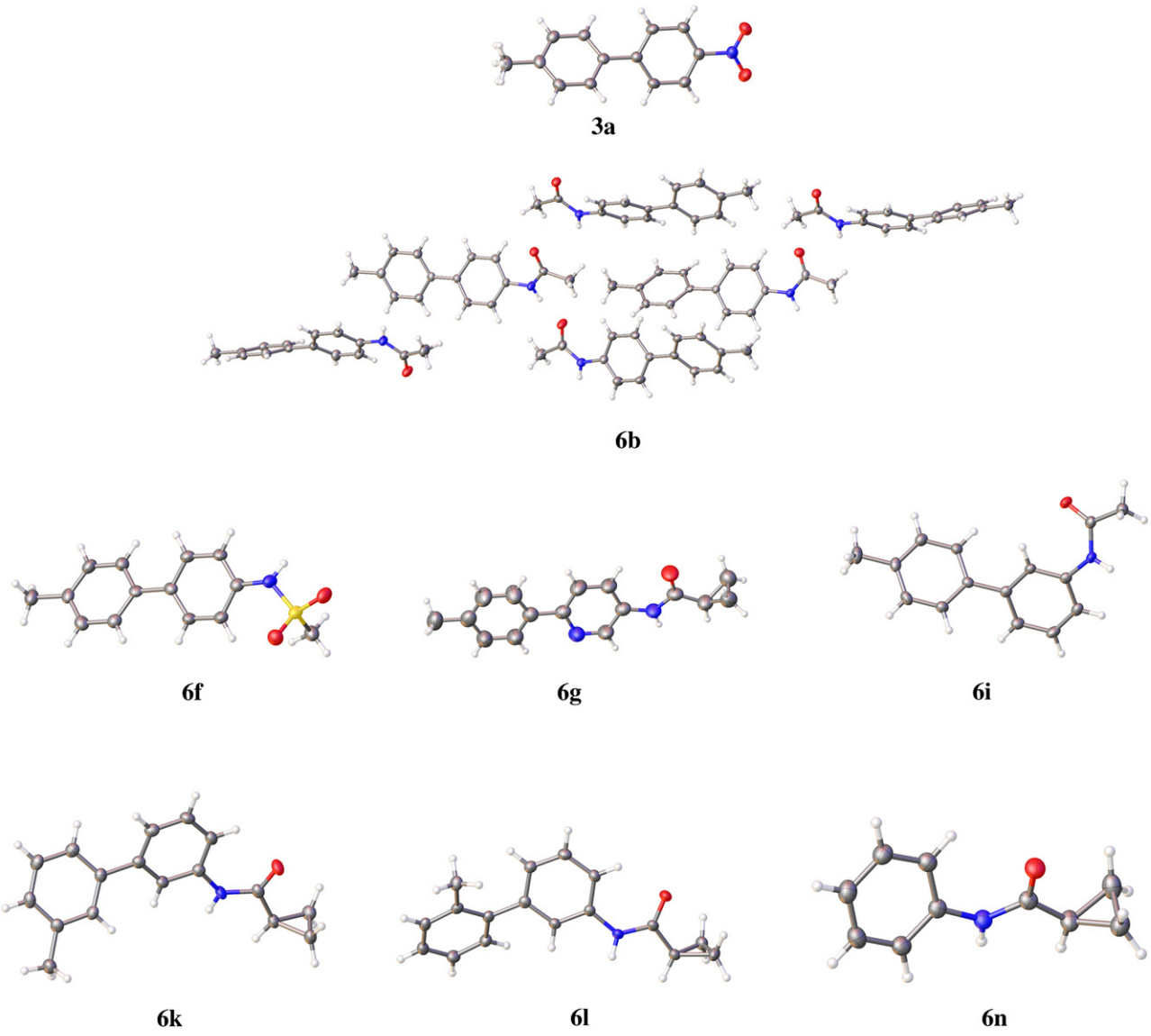


Fig. 1. Crystal structure of **3a**, **6b**, **6f**, **6i**, **6k**, **6l**, **6g** and **6n**.

sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give 264 mg of crude product, which was purified by chromatography on silica gel, hexane/EtOAc 9:1–8:2, to give 203 mg of the pure expected product as an off-white (95% yield). The product was crystallised from CH_2Cl_2 and gave beige crystals. Mp: 131–133 °C. IR (cm^{-1}): 3104, 3080, 2920, 2846, 1594, 1511, 1484, 1325, 1295, 1107, 821, 752, 696. ^1H NMR ($CDCl_3$) δ (ppm): 8.28 (d, 2H, J=8.8 Hz), 7.72 (d, 2H, J=8.8 Hz), 7.53 (d, 2H, J=8.1 Hz), 7.31 (d, 2H, J=8.1 Hz), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 147.6, 146.6, 139.1, 135.1, 129.9 (2C), 127.5 (2C), 127.2 (2C), 124.1 (2C), 21.2. Elemental analysis found C, 72.9; H, 5.2; N, 6.3. $C_{13}H_{11}NO_2$ requires C, 73.2; H, 5.2; N, 6.6.

4.2.2. 5-Nitro-2-p-tolylpyridine ***3b***. Made as for **3a** except that 2-bromo-5-nitropyridine (**2b**) was used instead of **2a**. Yellow solid, 96 mg, (90% yield, 0.50 mmol scale). Crystallisation from CH_2Cl_2/MeOH. Mp: 132–133 °C. IR (cm^{-1}): 3075, 2847, 1595, 1572, 1518, 1506, 1462, 1341, 1119, 1013, 855, 820, 760. ^1H NMR ($CDCl_3$) δ (ppm): 9.47 (d, 1H, J=2.3 Hz), 8.50 (dd, 1H, J_1=2.3 Hz, J_2=9.2 Hz), 8.00 (d, 2H, J=8.2 Hz), 7.88 (d, 1H, J=9.2 Hz), 7.33 (d, 2H, J=8.2 Hz), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 162.5, 145.2, 142.6, 141.4, 134.3, 131.9, 129.9 (2C), 127.6 (2C), 119.6, 21.4. HRMS-ES (m/z) found 215.0812, calcd for $[C_{12}H_{10}N_2O_2+H]^+$ 215.0815. Elemental analysis found: C, 67.4; H, 4.7; N, 13.2. $C_{12}H_{10}N_2O_2$ requires C, 67.3; H, 4.7; N, 13.1.

4.3. General procedure for the nitro group reduction

*4.3.1. 4′-Methyl-4-aminobiphenyl (**4a**).* Compound **3a** (2.54 mmol, 541 mg) was dissolved in an EtOH/EtOAc 1:1 mixture (50 mL) and reduced by hydrogenation catalysed by Raney Nickel in an H-Cube at 65 °C at a flow rate of 0.8 mL/min, using full hydrogen mode. The solution obtained was concentrated under reduced pressure to give 480 mg of a yellow solid, which was purified by chromatography on silica gel, hexane/CH_2Cl_2 1:1, to give 440 mg of the pure expected product as an off-white solid (95% yield). Mp: 88–90 °C. IR (cm^{-1}): 3422, 3382, 3290, 3187, 3023, 2916, 2857, 1625, 1604, 1499, 1272, 1178, 1193, 1137, 804. ^1H NMR ($CDCl_3$) δ (ppm): 7.41 (d, 2H, J=8.8 Hz), 7.37 (d, 2H, J=8.8), 7.18 (d, 2H, J=8.3 Hz), 6.73 (d, 2H, J=8.3 Hz), 3.71–3.65 (brs, 2H, NH_2), 2.35 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 145.5, 138.3, 135.9, 131.6, 129.4 (2C), 127.8 (2C), 126.3 (2C), 115.4 (2C), 21.0. HRMS-ES (m/z) found 184.1117, calcd for

$[C_{13}H_{13}N+H]^+$ 184.1121. Elemental analysis found: C, 85.4; H, 7.2; N, 7.6. $C_{13}H_{13}N$ requires C, 85.2; H, 7.2; N, 7.6.

4.3.2. 6-p-Tolylpyridin-3-amine ***4b***. Off-white solid, 80 mg (99% yield, 0.44 mmol scale). Mp: 96–98 °C. IR (cm^{-1}): 3461, 3308, 3193, 3035, 2917, 1629, 1595, 1562, 1481, 1629, 1562, 1421, 1321, 1299, 1244, 1146, 1038, 1018, 816, 749, 646. ^1H NMR ($CDCl_3$) δ (ppm): 8.16 (d, 1H, J=2.7 Hz), 7.78 (d, 2H, J=8.2 Hz), 7.51 (d, 1H, J=8.7 Hz), 7.22 (d, 2H, J=8.2 Hz), 7.03 (dd, 1H, J_1=2.7 Hz, J_2=8.7 Hz), 3.74–3.65 (brs, 2H, NH_2), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 148.1, 141.1, 137.6, 136.9, 136.6, 129.4 (2C), 125.9 (2C), 122.5, 120.5, 21.2. HRMS-ES (m/z) found 185.1071, calcd for $[C_{12}H_{12}N_2+H]^+$ 185.1073. Elemental analysis found C, 78.0; H, 6.6; N, 15.0. $C_{12}H_{12}N_2$ requires C, 78.2; H, 6.6; N, 15.2.

4.4. General amide coupling procedure

4.4.1. N-(4′-Methylbiphenyl-4-yl)acetamide ***6b***. Compound **4a** (0.33 mmol, 60 mg), **5b** (0.70 mmol, 1.104 g mL^{-1}, 50 μL), PS-NMM (0.70 mmol, 175 mg) and CH_2Cl_2 (10 mL) were stirred at rt for 48 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography on silica gel, CH_2Cl_2/EtOAc 9:1, to give 77 mg of the pure expected product as an off-white solid (99% yield). Crystallisation from CH_2Cl_2/MeOH. Mp: 208–210 °C. IR (cm^{-1}): 3130, 3109, 3030, 2915, 2855, 1605, 1530, 1498, 1324, 1119, 1066, 920, 844, 811, 719. ^1H NMR ($CDCl_3$) δ (ppm): 7.57–7.51 (m, 4H), 7.46 (d, 2H, J=8.4 Hz), 7.23 (d, 2H, J=8.4 Hz), 7.21–7.17 (m, 1H), 2.39 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.2, 137.6, 137.2, 136.9 (2C), 129.5 (2C), 127.4 (2C), 126.7 (2C), 120.1 (2C), 24.6, 21.1. HRMS-ES (m/z) found 226.1220, calcd for $[C_{15}H_{15}NO+H]^+$ 226.1226. Elemental analysis found C, 80.0; H, 6.8; N, 6.6. $C_{15}H_{15}NO$ requires C, 80.0; H, 6.7; N, 6.2.

4.4.2. Methyl 3-(4′-methylbiphenyl-4-ylamino)-3-oxopropanoate ***6c***. White solid, 123 mg, (97% yield, 0.45 mmol scale). Crystallisation from CH_2Cl_2/MeOH. Mp: 158–160 °C. IR (cm^{-1}): 3280, 3029, 2954, 2919, 1741, 1654, 1602, 1536, 1500, 1434, 1417, 1346, 1277, 1249, 1150, 1018, 806. ^1H NMR ($CDCl_3$) δ (ppm): 9.21–9.07 (brs, 1H), 7.55 (d, 2H, J=9.0 Hz), 7.48 (d, 2H, J=9.0 Hz), 7.40 (d, 2H, J=8.0 Hz), 7.17 (d, 2H, J=8.0 Hz), 3.75 (s, 3H), 3.44 (s, 2H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 170.5, 162.6, 137.6, 137.4, 136.9, 136.4, 129.5 (2C), 127.4 (2C), 126.7 (2C), 120.4 (2C), 52.7, 41.2, 21.1. HRMS-ES (m/z) found 284.1280, calcd for $[C_{17}H_{17}NO_3+H]^+$ 284.1281. Elemental analysis found C, 71.9; H, 6.2; N, 4.7. $C_{17}H_{17}NO_3$ requires C, 72.1; H, 6.1; N, 4.9.

4.4.3. 2-(Dimethylamino)-N-(4′-methylbiphenyl-4-yl)acetamide ***6d***. White solid, 95 mg, (81% yield, 0.44 mmol scale). Crystallisation from CH_2Cl_2/MeOH. Mp: 99–100 °C. IR (cm^{-1}): 3283, 3027, 2977, 2947, 2817, 2763, 1669, 1588, 1502, 1471, 1417, 1397, 1323, 1269, 1143, 1049, 986, 804, 732. ^1H NMR ($CDCl_3$) δ (ppm): 9.24–9.08 (brs, 1H), 7.65 (d, 2H, J=8.6 Hz), 7.55 (d, 2H, J=8.6 Hz), 7.47 (d, 2H, J=8.0 Hz), 7.23 (d, 2H, J=8.0 Hz), 3.09 (s, 2H), 2.42–2.36 (m, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.7, 137.7, 136.9, 136.8, 136.7, 129.5 (2C), 127.4 (2C), 126.7 (2C), 119.7 (2C), 63.7, 46.0 (2C), 21.1. HRMS-ES (m/z) found 269.1651, calcd for $[C_{17}H_{20}N_2O+H]^+$ 269.1648. Elemental analysis found C, 76.0; H, 7.5; N, 10.2. $C_{17}H_{20}N_2O$ requires C, 76.1; H, 7.5; N, 10.4.

4.4.4. N-(4′-Methylbiphenyl-4-yl)benzamide ***6e***. White solid, 115 mg (91% yield, 0.44 mmol scale). Mp: 214–215 °C. IR (cm^{-1}): 3346, 3050, 3032, 2912, 2855, 1652, 1595, 1514, 1397, 1252, 1139, 1026, 1003, 840, 805, 711, 691. ^1H NMR (DMSO-d_6) δ (ppm): 10.39–10.26 (brs, 1H), 7.97 (d, 2H, J=8.6 Hz), 7.87 (d, 2H, J=8.6 Hz), 7.65 (d, 2H, J=9.0 Hz), 7.61–7.51 (m, 5H), 7.26 (d, 2H, J=8.2 Hz), 2.34 (s, 3H). ^{13}C NMR (DMSO-d_6) δ (ppm): 165.5, 138.4, 136.8, 136.3, 135.2, 134.9, 131.6, 129.5 (2C), 128.4 (2C), 127.7 (2C), 126.5 (2C), 126.1 (2C), 120.6 (2C), 20.7. HRMS-ES (m/z) found 288.1384, calcd for $[C_{20}H_{17}NO+H]^+$ 288.1383. Elemental analysis found C, 83.2; H, 6.0; N, 4.7. $C_{20}H_{17}NO$ requires C, 83.6, H, 6.0, N, 4.9.

4.4.5. N-(4′-Methylbiphenyl-4-yl)methanesulfonamide ***6f***. White solid, 94 mg (82% yield, 0.44 mmol scale). Crystallisation from CH_2Cl_2/MeOH. Mp: 175–180 °C. IR (cm^{-1}): 3273, 3027, 2938, 2864, 1610, 1500, 1465, 1450, 1407, 1394, 1332, 1300, 1149, 969, 924, 838, 805, 752. ^1H NMR ($CDCl_3$) δ (ppm): 7.55 (d, 2H, J=8.4 Hz), 7.44 (d, 2H, J=8.4 Hz), 7.28–7.21 (m, 4H), 6.37–6.29 (brs, 1H), 3.03 (s, 3H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 138.6, 137.3, 137.1, 135.5, 129.6 (2C), 128.2 (2C), 126.7 (2C), 121.3 (2C), 39.5, 21.1. Elemental analysis found C, 63.7; H, 5.9; N, 5.3. $C_{14}H_{15}NO_2S$ requires C, 64.3; H, 5.8; N, 5.4.

4.4.6. N-(6-p-Tolylpyridin-3-yl)cyclopropanecarboxamide ***6g***. White solid, 26 mg (34% yield, 0.30 mmol scale). Crystallisation from CH_2Cl_2/MeOH. Mp: 213–215 °C. IR (cm^{-1}): 3288, 3013, 2918, 2966, 1659, 1601, 1538, 1509, 1478, 1397, 1368, 1286, 1198, 1183, 1033, 953, 811. ^1H NMR ($CDCl_3$) δ (ppm): 8.62–8.52 (brs, 1H), 8.25 (d, 1H, J=8.7 Hz), 7.85 (d, 2H, J=7.9 Hz), 7.68 (d, 1H, J=8.7 Hz), 7.50–7.44 (m, 1H), 7.26 (d, 2H, J=7.9 Hz), 2.40 (s, 3H), 1.59–1.52 (m, 1H), 1.16–1.11 (m, 2H), 0.93–0.88 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 172.3, 140.4, 138.6, 136.1, 133.4, 129.5 (3C), 127.8, 126.4 (2C), 120.2, 21.4, 15.8, 8.3 (2C). HRMS-ES (m/z) found 253.1332, calcd for $[C_{16}H_{16}N_2O+H]^+$ 253.1335. Elemental analysis found C, 75.8; H, 6.4; N, 11.0. $C_{16}H_{16}N_2O$ requires C, 76.2; H, 6.4; N, 11.1.

4.4.7. N-(4′-Methylbiphenyl-3-yl)cyclopropanecarboxamide ***6h***. White solid, 186 mg (74% yield, 1.00 mmol scale). Crystallisation from CH_2Cl_2/MeOH. Mp: 183–185 °C. IR (cm^{-1}): 3279, 3244, 3019, 2919, 1655, 1610, 1556, 1480, 1418, 1384, 1310, 1232, 962, 865, 816, 735, 692. ^1H NMR ($CDCl_3$) δ (ppm): 7.83–7.70 (brs, 1H), 7.50–7.42 (m, 3H), 7.41–7.36 (m, 1H), 7.36 (dd, 1H, $J_{1\text{ and }2}$=7.8 Hz), 7.31 (d, 1H, J=7.8 Hz), 7.22 (d, 2H, J=8.2 Hz), 2.38 (s, 3H), 1.56–1.45 (m, 1H), 1.14–1.07 (m, 2H), 0.89–0.80 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.9, 142.1, 138.6, 137.9, 137.4, 129.5 (2C), 129.4, 127.1 (2C), 122.7, 118.3 (2C), 21.2, 15.9, 8.1 (2C). HRMS (m/z) found 252.1386, calcd for $[C_{17}H_{17}NO+H]^+$ 252.1383. Elemental analysis (%) found C, 81.1; H, 6.6; N, 5.3, $C_{17}H_{17}NO$ requires C, 81.2; H, 6.8; N, 5.6.

4.4.8. N-(4′-Methylbiphenyl-3-yl)acetamide ***6i***. White solid, 164 mg (89% yield, 0.82 mmol scale). Crystallisation from CH_2Cl_2/MeOH. Mp: 138–141 °C. IR (cm^{-1}): 3260, 3063, 2919, 1666, 1609, 1555, 1485, 1417, 1364, 1316, 1260, 782, 692, 817. ^1H NMR ($CDCl_3$) δ (ppm): 7.72–7.66 (brs, 1H), 7.52–7.45 (m, 3H), 7.37 (dd, 1H, $J_{1\text{ and }2}$=7.6 Hz), 7.32 (d, 1H, J=7.6 Hz), 7.24 (d, 2H, J=8.0 Hz), 7.25–7.17 (brs, 1H), 2.39 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.3, 142.2, 138.3, 137.9, 137.4, 129.6 (2C), 129.4, 127.1 (2C), 123.1, 118.6, 118.5, 24.8, 21.2. HRMS-ES (m/z) found 226.1227, calcd for $[C_{15}H_{15}NO+H]^+$, 226.1226. Elemental analysis (%) found C, 79.8; H, 6.6; N, 6.1. $C_{15}H_{15}NO$ requires C, 80.0; H, 6.7; N, 6.2.

4.4.9. N-(4′-Methylbiphenyl-3-yl)methanesulfonamide ***6j***. White solid, 103 mg (40% yield, 1.00 mmol scale). Crystallisation from CH_2Cl_2/MeOH. Mp: 83–84 °C. IR (cm^{-1}): 3252, 3033, 2925, 1606, 1469, 1408, 1386, 1318, 1302, 1144, 967, 839, 881, 815, 783, 742, 964. ^1H NMR ($CDCl_3$) δ (ppm): 7.47 (d, 2H, J=8.0 Hz), 7.43–7.39 (m, 3H), 7.26 (d, 2H, J=8.0 Hz), 7.20–7.16 (m, 1H), 6.40–6.30 (brs, 1H), 3.04 (s, 3H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 143.0, 137.8, 137.1, 137.0, 130.1, 129.6 (2C), 127.0 (2C), 124.1, 119.2, 119.1, 39.5, 21.1.

Elemental analysis (%) found C, 64.2; H, 6.0; N, 5.6. $C_{14}H_{15}NO_2S$ requires C, 64.3; H, 5.8; N, 5.4.

4.4.10. N-(3′-Methylbiphenyl-3-yl)cyclopropanecarboxamide ***6k***. Beige solid, 69 mg (26% yield, 1.00 mmol scale). Crystallisation from CH_2Cl_2/MeOH. Mp: 164–167 °C. IR (cm^{-1}): 3289, 3087, 3017, 1655, 1609, 1554, 1484, 1385, 1405, 1417, 1234, 1197, 965, 877, 819, 792, 777, 706. ^1H NMR ($CDCl_3$) δ (ppm): 7.86–7.74 (brs, 1H), 7.51–7.26 (m, 7H), 7.16 (d, 1H, J=7.4 Hz), 2.40 (s, 3H), 1.65–1.39 (m, 1H), 1.14–1.06 (m, 2H), 0.89–0.81 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.9, 142.3, 140.7, 138.5, 138.3, 129.3, 128.6, 128.2, 128.0, 124.3, 122.9, 118.4 (2C), 21.5, 15.9, 8.0 (2C). Elemental analysis (%) found C, 80.6, H, 6.8, N, 5.5. $C_{17}H_{17}NO$ requires C, 81.2; H, 6.8; N, 5.6.

4.4.11. N-(2′-Methylbiphenyl-3-yl)cyclopropanecarboxamide ***6l***. White solid, 131 mg (52% yield, 1.00 mmol scale). Crystallisation from CH_2Cl_2/MeOH. Mp: 113–115 °C. IR (cm^{-1}): 3281, 3245, 3188, 3059, 3015, 2989, 2958, 1656, 1608, 1556, 1493, 1410, 1387, 1309, 1229, 1197, 960, 886, 867, 758, 735, 702. ^1H NMR ($CDCl_3$) δ (ppm): 7.52 (d, 1H, J=7.8 Hz), 7.45 (s, 1H), 7.39–7.30 (m, 2H), 7.26–7.20 (m, 4H), 7.06 (d, 1H, J=7.4 Hz), 2.28 (s, 3H), 1.55–1.43 (m, 1H), 1.12–1.07 (m, 2H), 0.88–0.82 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.8, 142.8, 141.4, 137.8, 135.3, 130.3, 129.7, 128.7, 127.4, 125.7, 125.0, 120.5, 118.1, 20.5, 15.8, 8.0 (2C). Elemental analysis (%) found C, 81.0; H, 6.9; N, 5.6. $C_{17}H_{17}NO$ requires C, 81.2; H, 6.8; N, 5.6.

4.4.12. N-(2′-Methylbiphenyl-3-yl)acetamide ***6m***. White solid, 103 mg (46% yield, 1 mmol scale). Crystallisation from CH_2Cl_2/MeOH. Mp: 86–89 °C. IR (cm^{-1}): 3310, 3058, 2924, 2855, 1663, 1586, 1549, 1472, 1419, 1363, 1318, 1254, 895, 785, 759, 725, 700. ^1H NMR ($CDCl_3$) δ (ppm): 7.73–7.68 (m, 1H), 7.56–7.50 (m, 2H), 7.42 (s, 1H), 7.35 (dd, 1H, J=7.8 Hz), 7.30–7.17 (m, 3H), 7.07 (d, 1H, J=7.4 Hz), 2.27 (s, 3H), 2.18 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.2, 142.8, 141.4, 137.6, 135.3, 130.3, 129.7, 128.7, 127.4, 125.7, 125.3, 120.6, 118.3, 24.7, 20.4. Found C, 79.2; H, 6.8; N, 6.2. $C_{15}H_{15}ON.0.1CH_3OH$ requires C, 79.4; H, 6.8; N, 6.1.

4.4.13. N-Phenylcyclopropanecarboxamide ***6n***. White solid, 87 mg (90% yield, 0.60 mmol scale). Crystallisation from CH_2Cl_2. Mp: 102–104 °C. IR (cm^{-1}): 3286, 3254, 3063, 3007, 1657, 1596, 1537, 1499, 1486, 1437, 1400, 1304, 1252, 1197, 1182, 950, 745, 694. ^1H NMR ($CDCl_3$) δ (ppm): 7.50 (d, 2H, J=7.8 Hz), 7.43–7.26 (m, 1H), 7.31 (dd, 2H, $J_{1\text{ and }2}$=7.8 Hz), 7.09 (dd, 1H, $J_{1\text{ and }2}$=7.8 Hz), 1.56–1.43 (m, 1H), 1.13–1.06 (m, 2H), 0.89–0.80 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 171.9, 138.2, 129.1 (2C), 124.1, 119.8 (2C), 15.9, 8.0 (2C). HRMS-ES (m/z) found 162.0911, calcd for $[C_{10}H_{11}ON+H]^+$ 162.0913. Found C, 74.3; H, 6.9; N, 8.6. $C_{10}H_{11}ON$ requires C, 74.5; H, 6.9; N, 8.7.

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